Remarks

In the Office Action dated September 19, 2005, claims 1-32, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-32 remain in this application and new claims 33-37 have been added to the application.

Claims 6-32 were rejected under 35 USC §112, second paragraph as indefinite. Claim 6 has been amended to indicate that the rifaximin is dried to the desired water content to produce the different polymorphs. The present inventors have unexpectedly discovered that the alpha and beta forms are formed depending on the water content. Regarding claims 21-25, these claims have been amended to indicate that the composition contains a "specified" amount of the recited forms and to recite the descriptions of the polymorphs as in claims 1, 3 and 5. Claims 29-31 have been amended to recite "pharmaceutical" composition. Regarding claim 32, applicants point out that claim 1 is directed to purified rifaximin alpha but claim 32 is directed to a pharmaceutical composition containing purified rifaximin and suitable excipients. Thus, these claims are not duplicates of each other.

Claims 1-5 were rejected under 35 USC §102(b) as anticipated by Cannata (U.S. Patent No. 4,557,866) or Marchi (U.S. Patent No. 4,341,785). Neither Cannata or Marchi suggest or disclose that rifaximin exists as different polymorphs and thus the rifaximin produced according to Cannata and Marchi were not tested for polymorphs until after the present invention was made.

Sample batches, which were made according to Cannata and/or Marchi in 2000-2001, were tested and found to contain a mixture of alpha and beta forms, alpha and epsilon forms, delta form alone or epsilon form alone. Some examples of the results of the testing are below.

(i) A batch manufactured in 2001 and measured by X-ray diffractogram in 2002, turned out to be entirely composed of a polymorph subsequently defined "delta polymorph" (see Figure 1 attached to Dr. Viscomi's declaration).

(ii) A batch manufactured in 2001, later analyzed in 2002, consisted exclusively of the epsilon form (see Figure 2 attached to Dr. Viscomi's declaration).

(iii) Another batch manufactured in 2001, instead, turned out to be a mixture of the alpha and epsilon forms (see Figure 3 attached to Dr. Viscomi's declaration).

(iv) A batch manufactured in 2004 (batch no. 2000 0827) and retested in 2005 was a mixture of the alpha and delta forms (see Figure 4 attached to Dr. Viscomi's declaration).

The present inventors have also found that the crystalline forms resulting from Cannata and Marchi are susceptible to transition from one form to another. This has been demonstrated by means of the following examples, referring to batch no. 2000 0827 manufactured in 2000. A sample of this batch was stored in a small conventional screw-cap glass container; the sample was analyzed using the X-ray diffractograms over time.

(1) The diffractogram of June 2000 revealed that the rifaximin was in the alpha form with a certain amount of the beta form (see Figure 5 attached to Dr. Viscomi's declaration).

(2) The diffractogram of May 2001, showed a mixture of the alpha and epsilon forms (see Figure 6 attached to Dr. Viscomi's declaration).

(3) Finally, the diffractogram of February 2002 corresponded to a mixture of the epsilon and beta forms (see Figure 7 attached to Dr. Viscomi's declaration).

In addition, the humidity content of the sample, due to repeated opening of the container and the collection time of the samples under non-controlled humidity conditions, had increased from the initial value of 1.3% to the final value of 4.5%, which was enough to change one rifaximin form to another.

Thus, it was not known prior to the present invention that the desired pure polymorphs could be obtained by optimizing the various parameters of drying, e.g. temperature, time and other conditions. As an example, during the drying of batch no. 0200256263 huge clots of product accidentally formed, preventing the uniform drying of the polymorph, which eventually was shown to be a mixture of the alpha and beta forms (see Figure 8 attached to Dr. Viscomi's declaration). It was necessary to carry out the crystallization and drying processes again in order to obtain the pure polymorph.

In addition, the different polymorphs have different intrinsic dissolution rates as discussed in application serial no. 11/135,651. This application highlights the potential risk of resistance induction which in the case of antibiotics can

occur at very low plasma concentrations, even 0.1 mg/ml. The differences which are reported, which in absolute terms do not seem very significant, are very important from a microbiological standpoint, as an adsorption of 0.1 mg is very different from an adsorption of 0.07 mg, especially for products like Rifaximin which are defined as a local acting agent. As discussed in application serial no. 11/135,651, it has now been found that the level of systemic rifaximin adsorption can be modulated by administering distinct polymorphic forms of rifaximin, e.g., rifaximin form alpha, rifaximin beta and rifaximin gamma. It is possible to have a difference in the adsorption of almost 600 fold in the range from 0.001 to 1 μg/ml in blood depending on which polymorph or combination of polymorphs is administered. In view of the differences in adsorption rates for the different polymorphs, applicants contend that the pure polymorphs or compositions containing specified amounts of the pure polymorphs according to the present invention would have a different utility than the undetermined polymorphs and mixtures in the prior art. In view of the above discussion and Dr. Viscomi's attached declaration, applicants request that these rejections be withdrawn.

Applicants respectfully submit that all of claims 1-37 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By _____

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